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A Retrospective Analysis of Hypothyroidism in Carcinoma Breast patients receiving Supraclavicular Radiation with Different Fractionation Schedules in a Single Institution.

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Abstract: *The retrospective analysis of hypothyroidism in carcinoma breast patients receiving supraclavicular radiation with different fractionation schedule in a single institution.*
Materials & Methods
Between July 2014 and April 2016, data of 128 patients with breast carcinoma who were treated at the Department of Radiotherapy, N.R.S Medical College, Kolkata, with supraclavicular area radiation with different fractionation schedule were retrospectively analyzed for appearance of hypothyroidism. The two types of fractionation schedules that used were 50 Gy / 25 # / 5 weeks and 42.56 Gy/ 16 # / 3.1 weeks.
Results
The incidence of hypothyroidism after radiation to the supraclavicular fossa was found to be 19.7% in case of conventional radiation and 17.7% in case of hypofractionated radiation respectively with no statistically significant difference in incidence rates.
Conclusion
Our study despite its limitations provides useful information about the risk of hypothyroidism after radiation therapy for supraclavicular area in breast cancer patients with the conventional and hypofractionated regime which may be useful for both treatment planning and the follow-up after treatment for future patients.
Keywords*: Breast Cancers, Fractionation,Hypothyroidism, Supraclavicular Radiotherapy;*

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I. Introduction

Breast cancer is the commonest cancer in women in India surpassing cervical cancer in recent year. Usually breast cancer patients require radiation for the treatment of the microscopic residual disease after operation. Adjuvant radiotherapy to post-operative bed and drainage area can reduce the locoregional recurrence rate from 30 % to 10.5 % and reduce the mortality rate by 5.4% at 20 years follow up.[1] Radiation therapy is usually given to chest wall and ipsilateral supraclavicular fossa in the neck. Unfortunately, the thyroid gland (partly) is covered in the radiation portal leading to the development of hypothyroidism often as a late effect. Hypothyroidism is a well-documented and well-known side effect of head and neck cancer and Hodgkin's lymphoma where the whole of the thyroid gland is encompassed in the radiation portal. [2,3,4]However, there is limited data on hypothyroidism following supraclavicular RT in breast cancer patients.

The radiation-induced hypothyroidism is due to both radiation-induced microvascular and macrovascular damage, directly, in and around the thyroid gland resulting in tissuehypoxemia. [5,6] Hypoxic thyroid cell result in reduced synthetic and secretory capacity of the gland itself. Radiation induced fibrosis of the gland's capsule prevent compensatory hypertrophy that worsens the situation. Symptoms of hypothyroidism are weakness and fatigue, dry rough skin, cold intolerance, alopecia, weight gain, memory loss and decreased mentation, neuropsychiatry disorders and other disorders affecting heart lung and other vital organs. Early diagnosis and proper treatment are absolute necessary to decrease the rate of morbidity and mortality.

The minimal thyroid gland TD 5/5 (tolerance dose for 5% hypothyroidism at 5 yrs.) is 20 Gy with total or partial irradiation by standard fractionation.[7] However, some studies reported a higher dose or even non-significant increase in incidence of hypothyroidism following supraclavicular RT.

Traditionally radiation to the tumour bed and supraclavicular fossa for adjuvant therapy of breast cancer was given with 50 Gy dose in 25 fractionations (conventional fractionation) over 5 weeks. Now a day's breast cancer is treated with hypofractionated radiotherapy more and more where a shortened course is used with larger fraction size e.g. 42.56 Gy in 16 fractionations over 3.1 weeks. this provides benefit to both patients and also has the logistic advantage of short treatment time. This improves compliance and cost of therapy.

Unfortunately, there are few studies comparing the effect of Supraclavicular radiation with different fractionated schedule of rt. Our aim is to analyse the incidence of hypothyroidism following supraclavicular RT by the 2 different fractionation schedules followed in our institution.

II. Material And Methods

2.1 Between July 2014 and April 2016, data of 128 patients with breast carcinoma who were treated at the Department of Radiotherapy, N.R.S Medical College, Kolkata, with supraclavicular area radiation as part of the treatment with different fractionation schedule were retrospectively analysed for appearance of hypothyroidism (both subclinical and clinical).The two types of fractionation schedules that were used were group A conventional fractionation (50 Gy / 25 # / 5 weeks) and group B hypofractionated schedule (42.56 Gy/ 16 # / 3.1 weeks). Al the patients received radiation with telecobalt machine Theratron 780 c., as per the departmental protocol patients had thyroid function test at 3 months, 6 months after completion of therapy and then 6-month interval thereafter for 3 years and then yearly.The patients were to be considered hypothyroid if the level of TSH was above the normal with low or normal T4 in the presence or absence of clinical features of hypothyroidism. The normal values used for our study were TSH 0.5–4.7 μU/ml and free T4 0.8–2.7 ng/dl. Clinical hypothyroidism has beenidentified by low free T4 and high thyroid stimulating hormone (TSH), and subclinical hypothyroidism by normal free T4 and high TSH.

2.2 Statistics

Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL) and Excel sheet (Microsoft). Chi-square test was used to ascertain the significance of differences between two arms.

III. Result

3.1 There were total 128 patients with 66 patients in conventional fractionated radiation to the supraclavicular area and 62 patients in hypofractionated radiation to the supraclavicular area. In conventional and hypofractionated arms, mean age of the patients were comparable (54.5 and 58.08 respectively) (p-value= 0.12). Patients were followed up for a median follow up period of 48 months (range30-54 months).

3.2 Incidence of hypothyroidism :A total of 13 (19.7%) patients out of 66 patients who had been treated by conventional fractionation to the supraclavicular area developed hypothyroidism and a total of 11 (17.7%) patients out of 62 patients who had been treated by hypofractionated radiation to the supraclavicular area developed hypothyroidism. All patients were put on thyroid replacement therapy. There is no statistically significant difference in incidence rates between two arms (P value= 0.78).

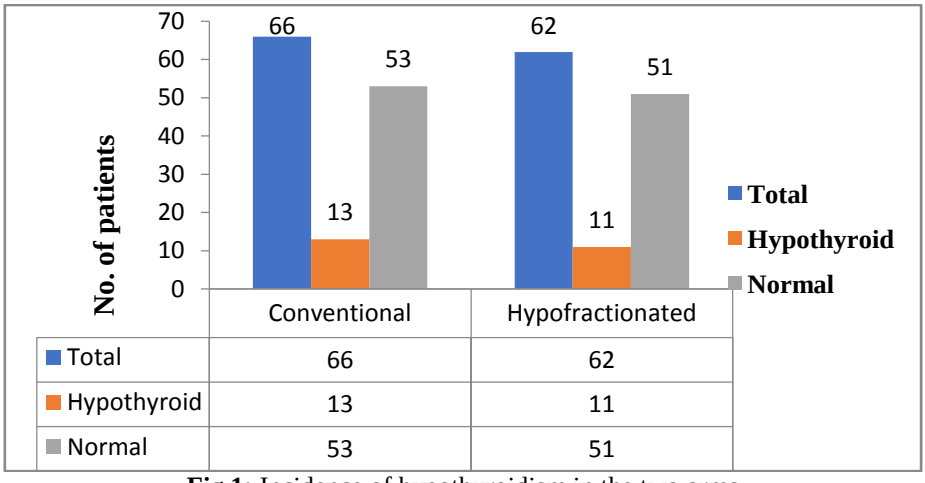

Fig 1: Incidence of hypothyroidism in the two arms

The cumulative incidence of hypothyroidism in the conventional arm at one, two, three years after supraclavicular area were2 (3.03%), 6 (9.09%) and 10 (15.15%) whereas the cumulative incidence of hypothyroidism in the hypofractionated radiation arm at one, two , three years after supraclavicular area were 3 (4.84%), 5 (8.06%) and 10 (16.13%). There is no statistically significant difference in prevalence of hypothyroidism, checked every 6 months, between two arms (P-value = 1.00). Incidences of new cases, as checked every 6 months are also comparable in the two arms (P-value= 0.922).

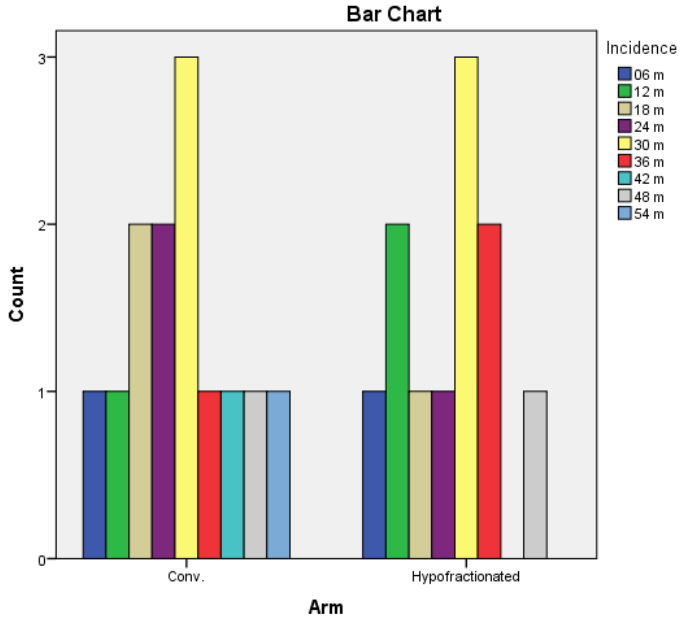

Fig 2: Bar chart showing incidence at the follow up intervals

		Incidence									Total
		06 m	12 m	18 m	24 m	30 m	36 m	42 m	48 m	54 m	
Arm	Conv.	1	1	2	2	3	1	1	1	1	13
	Hypofractionated	1	2	1	1	3	2	0	1	0	11
Total		2	3	3	3	6	3	1	2	1	24

Chart 1: chart showing incidence at the follow up intervals

The median time of onset of hypothyroidism was 30 months both in the conventional arm and in the hypofractionated radiation arm.

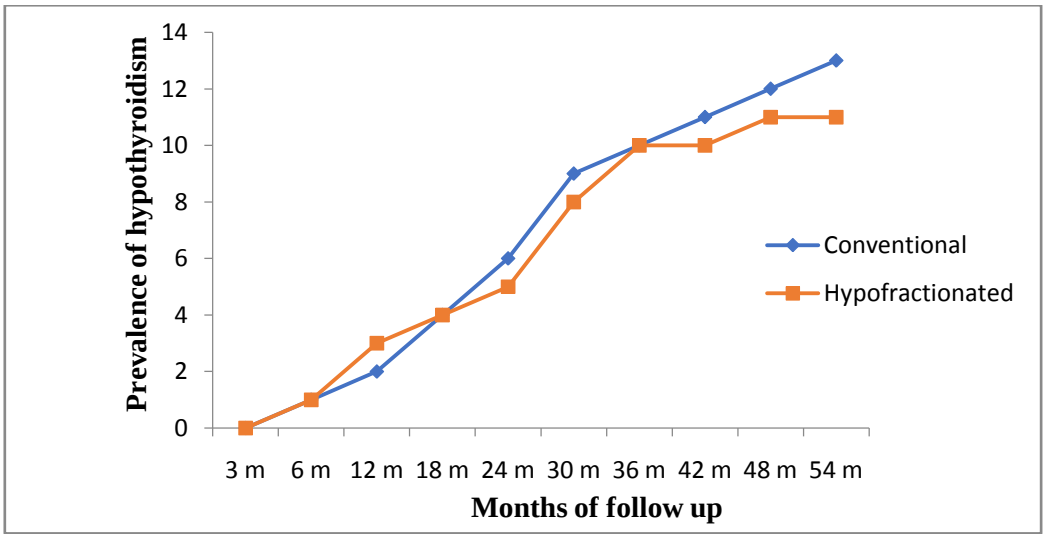

Fig 3: Prevalence of hypothyroidism in both arms

IV. Discussion

The prevalence of hypothyroidism after radiation to the supraclavicular fossa in different studies ranged from 6-18%. [8,9,10] In our studies we found 19.7% in case of conventional radiation and 17.7% in case of hypofractionated radiation which is consistent to the data. There is no statistically significant difference in

incidence rates between two arms (P value= 0.78). The cumulative incidence of hypothyroidism in the conventional arm at one, two, three years after supraclavicular area were 2 (3.03%) , 6 (9.09%) and 10 (15.15%) whereas the cumulative incidence of hypothyroidism in the hypofractionated radiation arm at one, two , three years after supraclavicular area were 3 (4.84%), 5 (8.06%) and 10 (16.13%). There is no statistically significant difference in prevalence of hypothyroidism, checked every 6 months, between two arms (P-value = 1.00). Incidences of new cases, as checked every 6 months are also comparable in the two arms (P-value= 0.922). The median time of onset of hypothyroidism was 30 months both in the conventional arm and in the hypofractionated radiation arm. This was consistent to other studies.

The radiation damage to thyroid is considered to be of two types subacute damage and late damage. Different factors have been studied for assessment of the correlation with hypothyroidism after radiation to the thyroid gland such as radiation dose, mean dose to thyroid gland, volume of thyroid gland receiving 30 GY (V30), and others. All these studies show different if sometimes contradictory results. However the general consensus is that supraclavicular radiation can cause hypothyroidism in previously euthyroid patients and V30 and Dmean have demonstrated maximum correlation to the development of hypothyroidism.[11]

Fractionation size as a correlation to hypothyroidism following supraclavicular radiation in case of breast cancer has been rarely studied. However, the increasing use of hypofractionated radiation for breast cancer has made us speculate about the different late toxicities that need to be addressed while planning for radiation. Our study was retrospectively done to ascertain this need and find out the need for reducing the radiation induced hypothyroidism. Our study showed us that hypothyroidism can occur in hypofractionated regime and the prevalence is almost similar to the conventional arm reducing our worry regarding the hypofractionated regime. Our study is unique because these data are probably the only data found regarding the prevalence of hypothyroidism following hypofractionated radiation to the supraclavicular area in breast cancer patients.

There are several possible limitations associated with our study such as absence of dose volume relationship of thyroid gland irradiated, small number of patients evaluated as well as the short follow-up duration. These patients were planned using conventional 2D planning and as such lacked these volumetric data. Also, the duration of follow-up was not long enough to thoroughly evaluate late toxicities. Nevertheless, our study provides useful information about the risk of hypothyroidism after radiation therapy for supraclavicular area in breast cancer patients with the conventional and hypofractionated regime which may be useful for both treatment planning and the follow-up after treatment for future patients. As such 3D conformal planning has already been started for breast irradiation in our institution and we are hopeful to broaden and further enrich our knowledge regarding hypothyroidism following supraclavicular radiation in case of breast cancer.

V. Conclusion

Our study, the first of its kind despite its limitations provides useful information about the risk of hypothyroidism after radiation therapy for supraclavicular area in breast cancer patients with the conventional and hypofractionated regime which may be useful for both treatment planning and the follow-up after treatment for future patients. The prevalence of hypothyroidism after radiation to the supraclavicular fossa for irradiation in breast cancer patients was found to be 19.7% in case of conventional radiation and 17.7% in case of hypofractionated radiation. There was no significant difference in incidence rate, time to develop hypothyroidism following and peak incidence. This unique study provides us with useful data regarding the prevalence of hypothyroidism following hypofractionated radiation to the supraclavicular area in breast cancer patients.

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